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# Hypospadias Prevalence and Trends in International Birth Defects Surveillance Systems, 1980 to 2010

Short Title: Hypospadias Prevalence and Trends

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**Abstract**

Background: Hypospadias is a common male birth defect that has shown widespread variation in reported prevalence estimates. Many countries have reported increasing trends over recent decades.

Objective: To analyze the prevalence and trends of hypospadias for 27 international programs over a 31-year period.

Design, Setting, and Participants: The study population included live births, stillbirths, and elective terminations of pregnancy diagnosed with hypospadias during 1980-2010 from 27 surveillance programs around the world.

Outcome Measurements and Statistical Analysis: We used joinpoint regression to analyze changes over time by international total hypospadias prevalence across programs, prevalence for each specific program, and prevalence across different degrees of severity of hypospadias.

Results and Limitations: The international total prevalence of hypospadias for all years was 20.9 (95% CI 19.2-22.6) per 10,000 births. The prevalence for each program ranged from 2.1 to 39.1 per 10,000 births. The international total prevalence increased 1.6 times during the study period, by 0.25 cases per 10,000 births per year ($p<0.05$). When analyzed separately, there were increasing trends for first-, second-, and third-degree hypospadias during the early 1990s to mid-2000s. The majority of programs (61.9%) had a significantly increasing trend during many of the years evaluated. Limitations include known differences in data collection methods across programs.

Conclusion: Although there have been changes in clinical practice and registry ascertainment over time in some countries, the consistency in the observed increasing trends across many programs and by degrees of severity suggest that the total prevalence of hypospadias may be increasing in many countries. This observation is contrary to some previous reports suggesting that the total prevalence of hypospadias was no longer increasing in recent decades.

Patient summary: We report on hypospadias prevalence and trends among 27 birth defects surveillance systems, which indicate that the prevalence of hypospadias continues to increase internationally.

**Key words:** hypospadias, prevalence, trend, joinpoint regression, International Clearinghouse for Birth Defects Surveillance and Research

**Abbreviations:** International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR); World Health Organization (WHO); British Pediatric Association (BPA); elective terminations of pregnancy for fetal anomaly (ETOPFA)

## INTRODUCTION

Hypospadias, which is caused by incomplete development of the urethra, is one of the most common congenital anomalies in male infants, with an estimated prevalence of 64.7 cases per 10,000 male live births in the United States (1). Hypospadias can have different degrees of clinical severity, as defined by the location of the urethral opening (2). Estimates of the prevalence of hypospadias vary across and within different geographical settings globally. The extent to which artefactual differences (e.g., differences in clinical practice, registry ascertainment, or case definitions) contribute to the observed prevalence differences is unknown. Moreover, there have been reports of increases in the prevalence of hypospadias in many countries, especially in the last decades of the 20th century (2-9). However, a number of countries have also reported that the prevalence has not increased in recent decades (3, 7, 9-17).

To better understand prevalence trends in recent years across the world, we evaluated hypospadias data in 27 birth defect surveillance programs participating in the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR).

## MATERIALS AND METHODS

### Data Collection

The ICBDSR is a World Health Organization-affiliated network of birth defects surveillance programs. The general methods of the ICBDSR are described elsewhere (18). Each of 27 surveillance programs identified hypospadias cases under their established protocol for births during 1980-2010 (case surveillance and selection methods are detailed in Appendix A).

**Statistical Analysis**

We calculated an international total prevalence of hypospadias per 10,000 births, defined as the total number of cases - live births, stillbirths, and elective terminations of pregnancy for fetal anomaly (ETOPFAs) - across all 27 programs divided by the total number of births (live births and stillbirths, regardless of sex) during the full study period (1980-2010). (We reported the total prevalence per male and female births for comparability with international prevalence reports of other birth defects). Because some programs did not have data between 1980 and 1999, we also calculated the international total prevalence of hypospadias per 10,000 births for a more recent period (2000-2010). Lastly, we calculated the total prevalence of hypospadias for each individual program during 1980-2010 and 2000-2010. The approximate 95% confidence interval (CI) was also calculated for all prevalence estimates. In addition, we determined the quartile (1, 2, 3, or 4) in which each program's total prevalence was located (e.g., programs in quartile 1 had a total prevalence within the lowest 25% of all the programs).

To visualize the data over time and to assess temporal changes in trends, we conducted analyses using joinpoint regression. Joinpoint regression is helpful for identifying linear trends in total prevalence over time that are restricted to sub-periods, rather than testing for linear trends only across the entire time period (19). This approach agnostically identifies joinpoints that parse the data into periods of varying sizes, based on the presence of similar linear trends within each period (19).

We conducted joinpoint regression for the total analytic group (all 27 programs) during the full study period. These analyses were repeated among a subset of 19 programs with three

characteristics (hereafter referred to as the "main sub-group"): (1) population-based ascertainment, (2) ascertainment of cases ≥1 year of age, and (3) ascertainment of cases from multiple sources. This sub-analysis was repeated again, only including 8 programs from the main sub-group with at least 30 years of data available. For comparison, we plotted the total prevalence of these 8 programs over time on the same figure.

We also conducted analyses separately for first-, second-, and third-degree hypospadias, including only the 12 programs for which the degree of severity was specified for ≥80% of cases. These analyses were repeated among 7 programs that were also in the main sub-group.

To better understand similarities and differences across programs, analyses were also performed during the full study period for each separate program. (Programs with < 11 years of data or with intermediate years of missing data were not included in this analysis, in order to meet the software's minimal requirements (19)).

All statistical tests were two-sided and we interpreted statistical significance based on a p-value < 0.05. Joinpoint regression analyses were performed using Joinpoint Trend Analysis Software (version 4.4.0.0) from the National Cancer Institute (20).

## RESULTS

### Program Characteristics

The characteristics of each program are summarized in Table 1. The majority of programs used population-based case identification (21 programs, 77.8%), registered cases up to 12 months of age or beyond (22 programs, 81.5%), and received notification of cases from

multiple sources (19 programs, 70.4%). There were only 12 programs (44.4%) that specified the degree of severity of hypospadias in ≥80% of cases.

**International Prevalence of Hypospadias**

For all programs combined, there were 36,127,500 births and 74,814 cases with hypospadias. The international total prevalence of hypospadias was 20.9 (95% CI: 19.2 -22.6) per 10,000 births among 27 programs of the ICBDSR during 1980-2010. For 2000–2010 specifically, the international total prevalence was 23.8 (95% CI: 22.1 - 25.5) per 10,000 births. Program-specific prevalences for 1980-2010 and 2000-2010 were tabulated (Table 2) and also presented in a histogram (Figure 1). Arkansas, USA had the highest total prevalence (39.1 cases per 10,000 births, 95% CI: 36.7 - 41.4), while Argentina had the lowest total prevalence (2.1 cases per 10,000 births, 95% CI: 1.1 - 4.8). Programs in Latin American countries (i.e., Argentina, Chile, Colombia, Mexico, and Costa Rica) had relatively lower total prevalence estimates than programs in other regions (Figure 1). The total prevalence in Europe was highly variable, ranging from 10.6 (France) to 37.4 (Lombardia, Italy) cases per 10,000 births. Only 4 (Atlanta, Georgia, USA; Mexico; Spain; Slovak Republic) out of 27 programs had a lower total prevalence in the recent period (2000-2010) than the whole period (1980-2010) (Figure 1).

The changes in the international total prevalence of hypospadias were visualized using joinpoint regression (Supplemental Figure 1), with joinpoints identified at 1996 and 1999. Since 1999, the total prevalence increased significantly by 0.25 cases per year ($p=0.001$). This analysis was repeated among the main sub-group (Figure 2a). For these programs, there was an increasing trend during the entire period 1980-2010, and this increase was statistically significant ($p<0.001$)

from 1980-1996 (0.19 cases per year) and 1999-2010 (0.34 cases per year). The analysis was repeated using data from the 8 programs with at least 30 years of data (Figure 2b). Among these programs, there was a 1.6 times increase in the total prevalence of hypospadias during the entire study period (from 1980-2010) by an average of 0.34 cases per year ($p<0.001$). Among these programs (Figure 2c) France had a relatively lower total prevalence during the entire period.

**Prevalence of Hypospadias by Degree of Severity**

Figures 3a, 3b, and 3c show the results from joinpoint regression analyses for first-, second-, and third-degree hypospadias. These analyses were restricted to programs with the degree of severity of hypospadias specified in ≥80% of cases (12 programs). Across all three degrees of severity, increasing trends were observed from the mid-1990s to the mid-2000s (Figure 3a, 3b, 3c). Similar trends were observed after repeating these analyses among 7 programs that were also in the main sub-group (Supplemental Figure 2a, 2b, 2c). Among these, 62.2% of cases had first-degree hypospadias, 20.1% had second-degree hypospadias, 4.5% had third-degree hypospadias, and 13.2% had an unspecified degree of severity (data not shown).

**Program-Specific Prevalence of Hypospadias**

Supplemental Figure 3 illustrates the results from the joinpoint regression for each program with at least 11 years of data (the software's minimal requirements). Five of the 27 programs were excluded from these analyses because they had less than 11 years of data (Argentina; Colombia; Chile; Canada [National]; Iran). Because the software required complete

data for each year analyzed, New Zealand was also excluded due to missing data for some years. Table 3 summarizes the trends from these analyses. Different trend patterns were observed across programs, including patterns of total prevalence increases during much or all of the study period for a number of programs. In fact, significant increases in the total prevalence of hypospadias were observed for 45.0% of the years of observation, whereas significant decreases in the total prevalence were observed for only 10.4% of the years of observation.

## DISCUSSION

Among 27 programs participating in the ICBDSR, the total prevalence of hypospadias was 20.9 per 10,000 births during 1980-2010, though it varied greatly by geographical region.

The international total prevalence of hypospadias increased during the entire study period, with significant increases from 2000 to 2010. When we restricted to programs among the main sub-group, the rates of increase were similar, though the time trend was significant over more years. The increasing trends were also consistent for most of the study period across all degrees of hypospadias clinical severity.

Our international total prevalence estimates of hypospadias were similar to those from previous studies, with many previous reported estimates from individual ICBDSR programs, including the United States (5), Australia (2), Germany (21), Northern Netherlands (21), Hungary (21), Malta (21), Spain (21) and Tuscany (21). For Latin American countries, our results were consistent with previous estimates from Argentina (22) and Mexico (23). In fact, all Latin American programs had a relatively low prevalence that fell within the lowest quartile of all participating programs. As the magnitude of the difference was quite large and consistent

across programs in Latin American countries, it is possible that the difference between Latin American countries and other countries may reflect true prevalence differences, perhaps related to differences in both genetic and non-genetic hypospadias risk factors.

As previously reported, programs in the United States and northern Europe had higher prevalence estimates (23).There have been reports of increases in the prevalence of hypospadias in many countries, particularly during the late 1960s until around the early 1990s in the U.S. and in Europe (reviewed in (24)). Our results for 1980 to the early 1990s seem consistent with these reported increases.

However, this increase was reported to stabilize or even decrease in more recent years in many, though not all, studies (3, 7, 21), whereas we detected an increase throughout this time. For example, separate reports from Washington State, USA (1987-2002 births) (17), New York State, USA (1983-1995 births) (13), Scotland (1988-1997 births) (11), Italy (2001-2004 births) (14), Finland (1970-1994 births) (12), and Europe (1980-1999 births from the EUROCAT Network) (7) did not indicate increases in the prevalence in more recent years. Further, individual reports from Spain (1996-2002 births) (16), Northern England (1993-2000 births) (10), and Japan (1985-1997 births) (15), suggested that the prevalence may have been decreasing in recent years. As expected, among these individual countries represented in our study (i.e., Finland, Italy, Spain, and other European regions), much of the corresponding data within these same time windows appeared similar in our data (i.e., not increasing). However, our results among all programs indicated an increase in the total prevalence during recent years. This difference was probably related to inclusion of a very large number of programs throughout a long (and in many instances, more recent) analysis period (1980-2010), as well as our use of joinpoint regression. However, it is noteworthy that these increases were not observed during

the entire period for each program, and it is important to remember that our findings were most influenced by the programs with larger sample sizes.

Although our study likely reflects a better estimate of global trends than smaller studies, it is likely that some of the observed prevalence increases in our study were artefactual, and reflect changes over time in how cases with hypospadias were identified and documented at the medical facility and/or were ascertained by the surveillance system (e.g., under-ascertainment in earlier years). While quality metrics for systematic assessment of birth defect surveillance have been recently proposed (25), many programs have not yet reported on these metrics (26, 27). Some ICBDSR systems implemented systematic surveillance changes during the study period (Supplemental Table 1), including a stronger focus on ascertaining less severe hypospadias cases in more recent years (21) and improvements in data collection over time.

Nevertheless, we still observed increasing prevalence time trends among the main sub-group, which represented 47.0% of total births across all ICBDSR programs. The data from these programs may have been less subject to bias compared to that from other sites, and these trends among this sub-group were similar to the trends observed in the full analytic group. This consistency suggests that much of the increasing trends in the prevalence of hypospadias may represent a true (non-artefactual) increase. However, consistent trends were not seen across every program.

It has been proposed that the observed prevalence increase might reflect increases in exposure to hypospadias risk factors over time (9). However, given the broad range of potentially relevant environmental and occupational exposures that could be responsible for the observed increase, as well as issues related to exposure dosage, timing, and other factors, it has been challenging to identify the main culprits. It is also possible that changes over time in the

distribution of other parental factors associated with hypospadias risk (e.g., parity, body mass index, maternal age, fertility treatments) may have influenced the prevalence over time, but data were not available to assess this possibility in our analyses (24). Further study of potential hypospadias risk factors, including genetic factors, endocrine disruptors, and other maternal and paternal exposures and characteristics may shed light on this possibility.

This study had some known limitations. First, it lacked uniformity in data collection across programs, which may have led to heterogeneity among cases across programs. Initiatives related to standardizing these methodologies across programs would be helpful to future work. Second, as individual-level data were not available, we could not adjust for differences in the distributions of hypospadias risk factors across countries, and this unmeasured confounding may have also partially accounted for the differences in hypospadias prevalence across programs. Third, the joinpoint regression modeled the data based on an assumption of linear trends across sub-periods, although it did not account for completely non-linear (e.g., exponential) trends. Nevertheless, this statistical approach did have more flexibility than a traditional assessment of a continuous prevalence estimate under the assumption of a linear change over an entire study period, which would not have been able to agnostically identify changes limited to study sub-periods. We also did not have data related to co-occurring congenital malformations (~88.5% of hypospadias is expected to be isolated in European countries (21)) or on hypospadias treatment; while we had data on hypospadias severity for some Programs, these data were not available for the majority of Programs.

Despite these limitations, this study has several important strengths. We analyzed data from surveillance programs across the world, which represents one of the largest case samples among published studies. Further, our data allowed us to look at trends over a thirty-one year

period. We also investigated the trends by differing degrees of severity and considered differences in characteristics of surveillance programs.

## CONCLUSION

Our results suggest that the international total prevalence of hypospadias increased during 1980-2010, and that these trends were probably not entirely artefactual. Considering these trends, it seems clear that further surveillance around hypospadias is critical.


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## CONFLICTS OF INTEREST

None

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

**Table 1** Summary of program characteristics, International Clearinghouse for Birth Defects Surveillance and Research

| Program | Delivery years | Total births | Ascertainment to at least 1 year | Population-based | Ascertainment from multiple sources | Degree of severity specified in ≥80% of cases |
|---|---|---|---|---|---|---|
| Argentina[c] | 2009-2010 | 42,136 | No | No | No | No |
| Australia[d] | 1980-2010 | 792,512 | Yes | Yes | Yes | Yes |
| Canada (National)[e] | 2005-2010 | 1,416,099 | No | Yes | No | No |
| Alberta, Canada[f] | 1980-2010 | 1,309,669 | Yes | Yes | Yes | No |
| Chile-Maule[g] | 2002-2010 | 119,900 | No | No | No | Yes |
| Colombia | 2001-2010 | 174,425 | Yes | No | No | Yes |
| Costa Rica[h] | 1987-2010 | 1,842,791 | Yes[a] | Yes | No | No |
| Czech Republic | 1980-2010 | 3,597,530 | Yes | Yes | Yes | Yes |
| Finland | 1993-2010 | 1,068,457 | Yes | Yes | Yes | Yes |
| France[i] | 1980-2010 | 2,819,326 | Yes | Yes | Yes | No |
| Germany[j] | 1987-2010 | 336,716 | Yes | Yes | Yes | No |
| Hungary | 1980-2010 | 3,507,915 | Yes | Yes | Yes | No |
| Iran[k] | 2005-2010 | 130,724 | Yes | No | Yes | -[b] |
| Lombardia, Italy | 1999-2010 | 179,484 | Yes | Yes | Yes | No |
| Tuscany, Italy[l] | 1992-2010 | 519,749 | Yes | Yes | Yes | No |
| Malta[m] | 1993-2010 | 77,261 | Yes | Yes | Yes | Yes |
| Mexico[n] | 1980-2010 | 1,093,745 | No | No | No | Yes |
| New Zealand | 1980-1993 1996-2010 | 1,638,216 | Yes | Yes | Yes | -[b] |
| Northern Netherlands | 1981-2010 | 496,810 | Yes | Yes | Yes | Yes |
| Slovak Republic | 1995-2010 | 902,372 | Yes | Yes | No | Yes |
| Spain[o] | 1980-2010 | 2,648,286 | No | No | No | Yes |
| Sweden | 1980-2010 | 3,166,009 | Yes | Yes | Yes | No |
| Arkansas, USA[p] | 1993-2010 | 684,001 | Yes | Yes | Yes | Yes |
| Atlanta, Georgia, USA[q] | 1980-2010 | 1,299,822 | Yes | Yes | Yes | No |
| Texas, USA | 1996-2010 | 5,216,949 | Yes | Yes | Yes | No |

| | | | | | | |
|---|---|---|---|---|---|---|
| Utah, USA[r] | 1999-2010 | 615,886 | Yes | Yes | Yes | Yes |
| Wales[s] | 1998-2010 | 430,710 | Yes | Yes | Yes | No |

a. For births during 2009 and later only
b. No information on degree of severity
c. National Network of Congenital Anomalies of Argentina (RENAC)
d. Western Australian Register of Developmental Anomalies
e. Canadian Congenital Anomalies Surveillance System
f. Alberta Congenital Anomalies Surveillance System
g. Registro de malformaciones congénitas del Servicio de Salud Maule (RRMC-SSM)
h. Centro de Registro de Enfermedades Congénitas
i. Registre des Malformations en Rhône-Alpes (REMERA)
j. Saxony-Anhalt
k. Tabriz Registry of Congenital Anomalies
l. Tuscan Registry of congenital defects (RTDC)
m. Malta Congenital Anomalies Register
n. Registration and Epidemiologic Surveillance of External Congenital Malformations (RYVEMCE)
o. Spanish Collaborative Study of Congenital Malformations (ECEMC)
p. Arkansas Reproductive Health Monitoring System
q. Metropolitan Atlanta Congenital Defects Program
r. Utah Birth Defect Network
s. Congenital Anomaly Register & Information Service for Wales

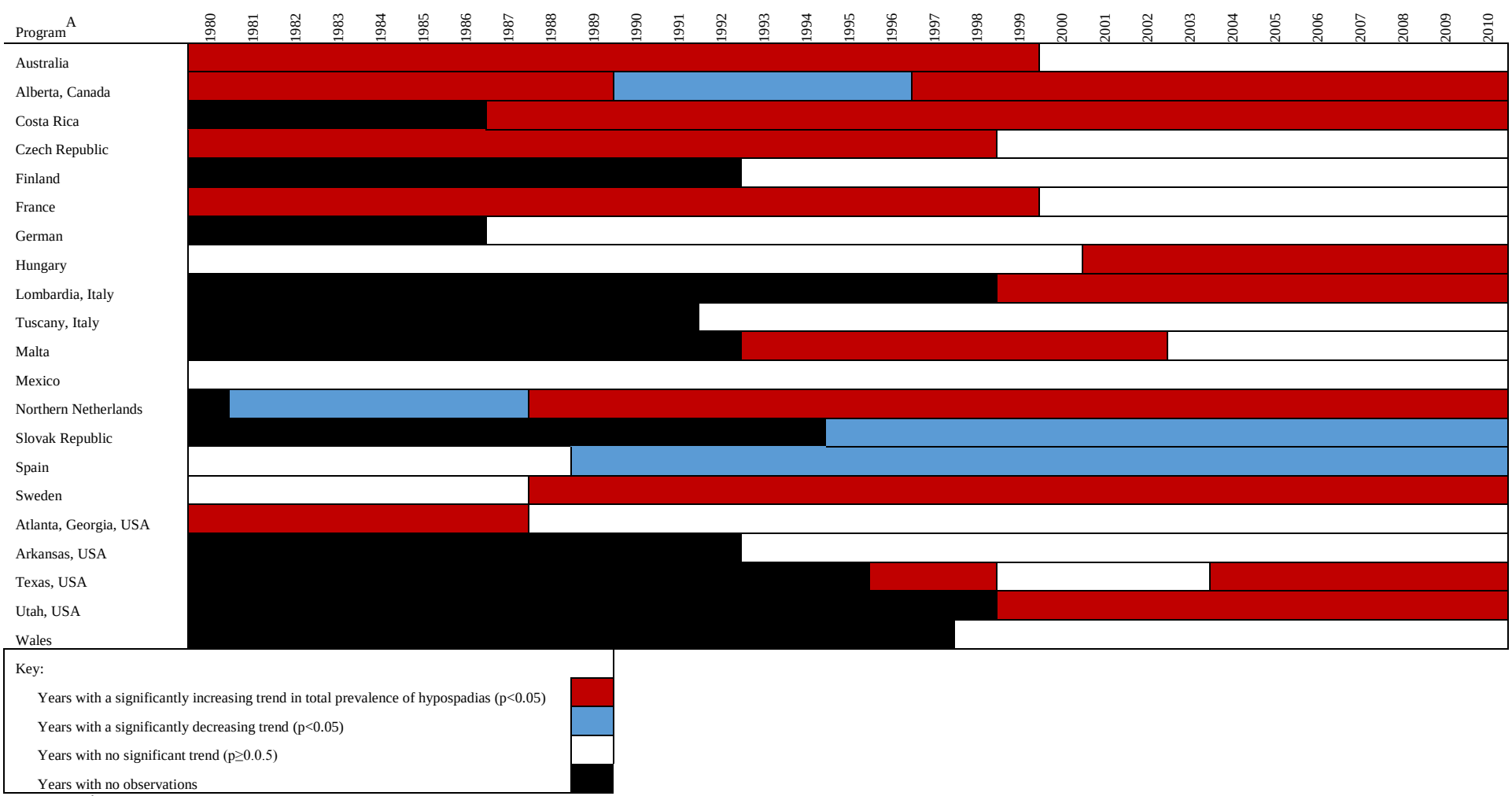
**Table 2** Total prevalence of hypospadias by program and time period, International Clearinghouse for Birth Defects Surveillance and Research

| Program | Delivery years | 1980-2010 | | | | 2000-2010 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Total prevalence per 10,000 | 95% Confidence Interval | | Quartile[a] | Total prevalence per 10,000 | 95% Confidence Interval | | Quartile[a] |
| | | | Lower | Upper | | | Lower | Upper | |
| Argentina | 2009-2010 | 2.14 | 1.11 | 4.83 | Q1 | 2.14 | 1.11 | 4.83 | Q1 |
| Australia | 1980-2010 | 33.68 | 31.58 | 35.34 | Q4 | 36.21 | 34.26 | 38.32 | Q4 |
| Canada (National) | 2005-2010 | 24.45 | 23.57 | 25.31 | Q3 | 24.45 | 23.57 | 25.31 | Q3 |
| Alberta, Canada | 1980-2010 | 21.13 | 19.77 | 22.31 | Q3 | 21.51 | 19.84 | 22.94 | Q2 |
| Chile-Maule | 2002-2010 | 8.26 | 6.62 | 9.85 | Q1 | 8.26 | 6.62 | 9.85 | Q1 |
| Colombia | 2001-2010 | 4.70 | 4.24 | 9.17 | Q1 | 4.70 | 4.24 | 9.17 | Q1 |
| Costa Rica | 1987-2010 | 4.77 | 4.24 | 5.42 | Q1 | 6.17 | 5.62 | 6.74 | Q1 |
| Czech Republic | 1980-2010 | 25.64 | 24.31 | 27.72 | Q3 | 31.86 | 30.29 | 32.70 | Q4 |
| Finland | 1993-2010 | 15.54 | 14.64 | 16.37 | Q2 | 15.97 | 14.74 | 17.11 | Q2 |
| France | 1980-2010 | 10.60 | 9.56 | 11.54 | Q1 | 12.55 | 11.67 | 13.49 | Q1 |
| Germany | 1987-2010 | 18.21 | 16.47 | 20.61 | Q2 | 19.32 | 17.09 | 21.65 | Q2 |
| Hungary | 1980-2010 | 22.30 | 21.17 | 23.92 | Q3 | 25.78 | 23.28 | 28.35 | Q3 |
| Iran | 2005-2010 | 13.69 | 8.70 | 18.41 | Q2 | 13.69 | 8.70 | 18.41 | Q2 |
| Lombardia, Italy | 1999-2010 | 37.38 | 33.42 | 40.92 | Q4 | 38.11 | 34.17 | 41.70 | Q4 |
| Tuscany, Italy | 1992-2010 | 19.22 | 17.15 | 21.16 | Q2 | 20.17 | 18.07 | 22.34 | Q2 |
| Malta | 1993-2010 | 29.64 | 22.46 | 38.88 | Q4 | 36.45 | 26.22 | 47.28 | Q4 |
| Mexico | 1980-2010 | 3.17 | 2.67 | 3.40 | Q1 | 2.75 | 2.04 | 3.53 | Q1 |
| New Zealand | 1980-1993 1996-2010 | 19.61 | 16.56 | 22.21 | Q2 | 27.02 | 24.65 | 29.70 | Q3 |
| Northern Netherlands | 1981-2010 | 15.06 | 12.80 | 17.05 | Q2 | 20.04 | 17.39 | 22.98 | Q2 |
| Slovak Republic | 1995-2010 | 21.98 | 20.30 | 23.81 | Q3 | 21.35 | 19.09 | 23.93 | Q2 |
| Spain | 1980-2010 | 14.75 | 14.12 | 16.34 | Q2 | 12.11 | 11.47 | 12.73 | Q1 |
| Sweden | 1980-2010 | 20.01 | 18.52 | 21.48 | Q3 | 24.97 | 23.39 | 26.26 | Q3 |
| Arkansas, USA | 1993-2010 | 39.11 | 36.67 | 41.43 | Q4 | 40.13 | 36.67 | 43.50 | Q4 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Atlanta, Georgia, USA | 1980-2010 | 31.28 | 29.66 | 32.70 | Q4 | 30.21 | 27.99 | 32.61 | Q3 |
| Texas, USA | 1996-2010 | 28.14 | 26.36 | 29.01 | Q3 | 28.57 | 27.32 | 29.75 | Q3 |
| Utah, USA | 1999-2010 | 30.59 | 28.03 | 32.84 | Q4 | 31.05 | 28.52 | 33.34 | Q3 |
| Wales | 1998-2010 | 31.65 | 30.57 | 32.80 | Q4 | 32.15 | 31.25 | 33.13 | Q4 |
| Total | - | 20.91 | 19.19 | 22.63 | - | 23.78 | 22.06 | 25.50 | - |

[a] Q1 corresponds to the lowest quartile of total prevalence and Q4 corresponds to the highest quartile

**Table 3** Annual trends in the total prevalence of hypospadias by program, 1980-2010




[A]Joinpoint regression was not performed for programs with <11 years of data (Argentina, Colombia, Chile, Canada [National], Iran) or any years of missing data during the period analyzed (New Zealand) due to the software's minimum data requirements.

**Supplemental Table 1.** Examples of reported systematic changes during 1980-2010 among International Clearinghouse for Birth Defects Surveillance and Research programs

| Program Location | Systematic change |
|---|---|
| Alberta, Canada | During the 1990s, case ascertainment dropped during a period of financial uncertainty. |
| Costa Rica | The age of ascertainment changed from ~3 days to 1 year in 2008. |
| Costa Rica | New training activities were implemented in the mid and late 2000's. |
| Czech Republic | Supplemental case ascertainment with additional newborn report records began in 2000. |
| Czech Republic | There were suspected changes in the awareness of hypospadias reporting requirements among neonatologists during the study period. |
| France | Data collection reportedly improved over time, as the number of data sources increased and other improvements in data quality were implemented. |
| Hungary | Reporting of documented birth defects became legally regulated and mandated in 1997, which resulted in higher numbers of most birth defects identified by early 2000. |
| Hungary | New procedures based on territorial representation were established in 2000, under which a different public health professional conducted the quality control of their respective county's data. |
| Many European programs | EUROCAT registry guidelines changed in 2005 to include isolated first degree hypospadias, which was previously excluded. |
| Many European programs | ICD classification and codes changed from ICD-9 752.6 to ICD-10 Q54.0-54.9 in many European countries around 1985, allowing for greater specification of severity classification. |

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Figure 1. Total prevalence of hypospadias (per 10,000) for International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) programs, grouped by world region, 1980-2010 and 2000-2010

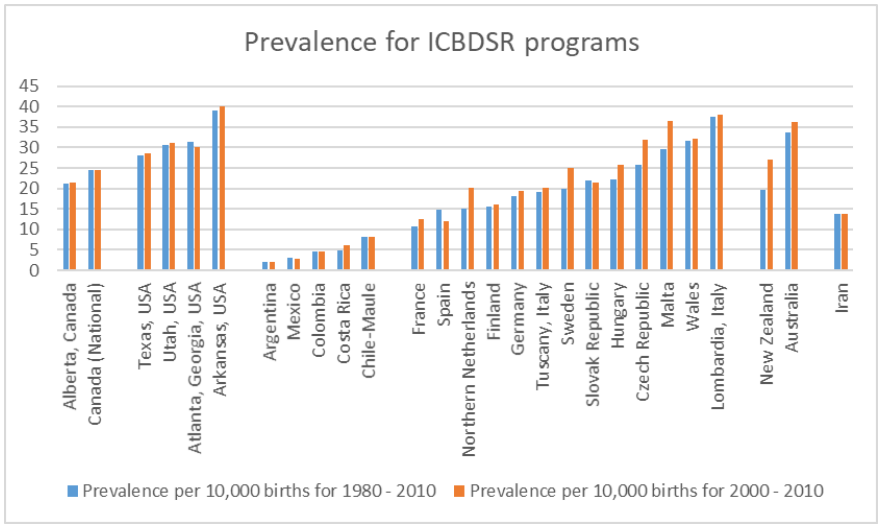
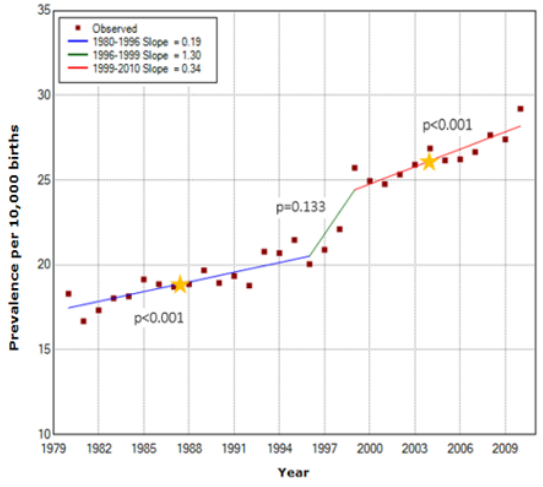
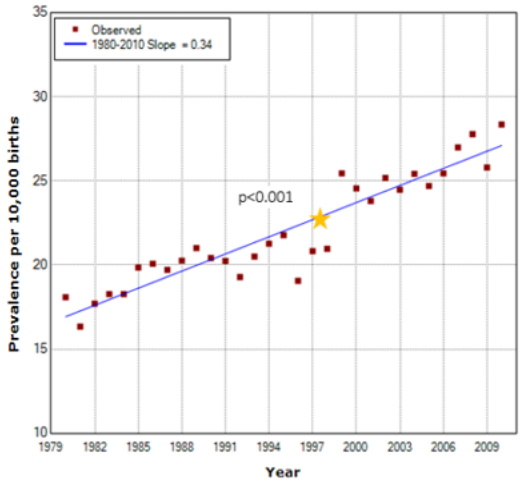


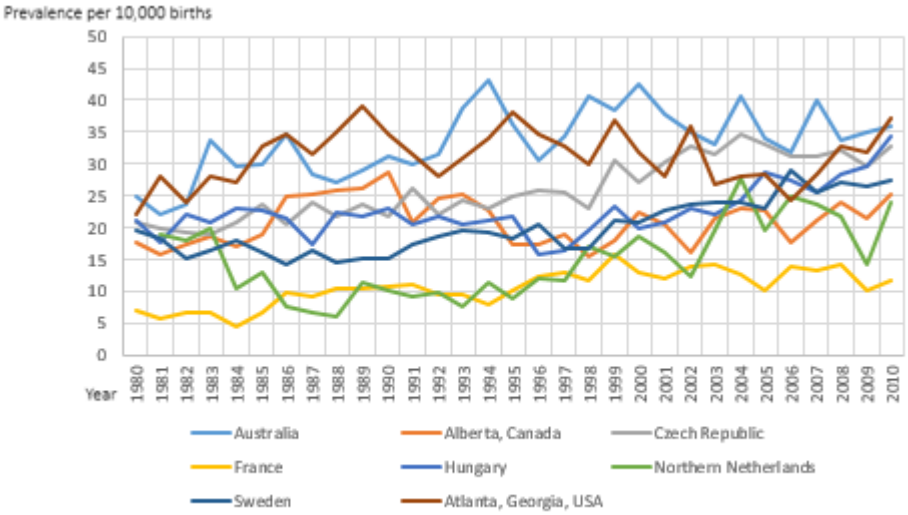
Figure 2 Trends in the international total prevalence of hypospadias among ICBDSR programs with select characteristics using joinpoint regression, 1980-2010.[a]




A)




B)

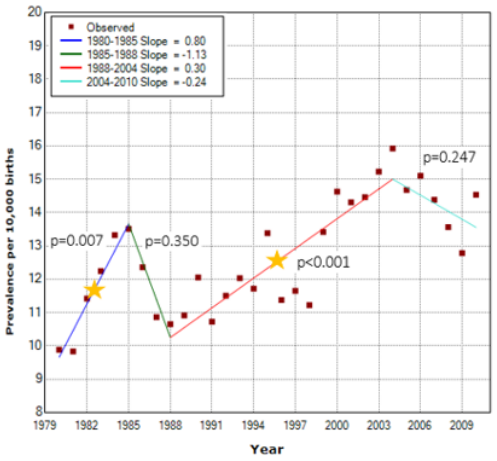



C)

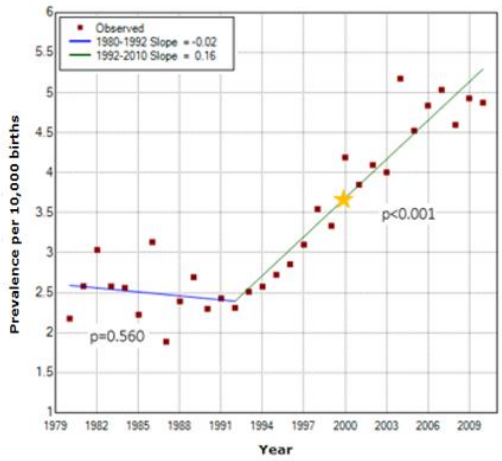
(A) Among 19 programs with 1) population-based ascertainment, 2) age of ascertainment ≥1 year, and 3) ascertainment from multiple sources. (B) Among 8 programs with 1) population-based ascertainment, 2) age of ascertainment ≥1 year, 3) ascertainment from multiple sources, and 4) at least 30 years of data. (C) Results by program, among 8 programs with 1) population-based ascertainment, 2) age of ascertainment ≥1 year, 3) ascertainment from multiple sources, and 4) at least 30 years data.

[a] Stars indicate joinpoints with statistically significant ($p<0.05$) trends.

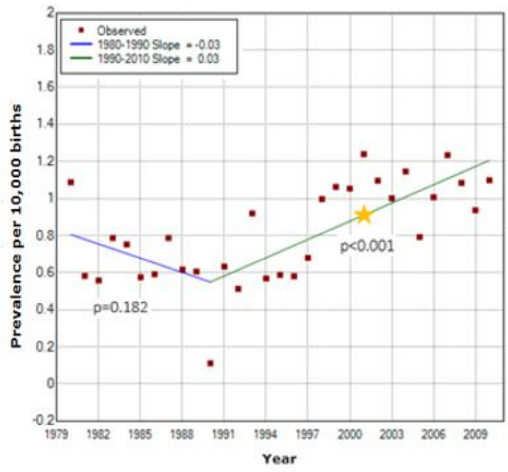
Figure 3. Trends in the international total prevalence of hypospadias for 12 ICBDSR programs by clinical degree of severity, 1980-2010.[a,b]




A)




B)



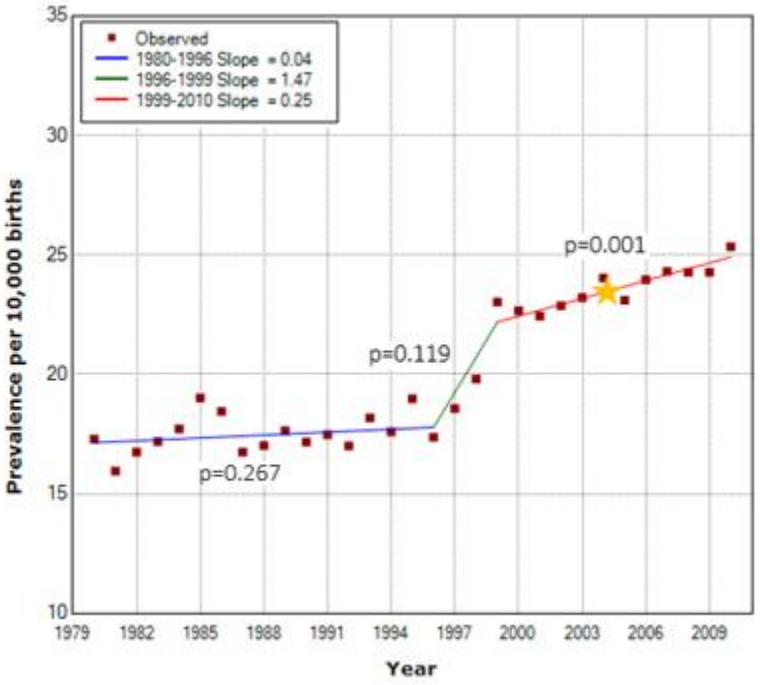

C)

A) First-degree hypospadias, B) second-degree hypospadias, and C) third-degree hypospadias

[a] Stars indicate joinpoints with statistically significant ($p<0.05$) trends.

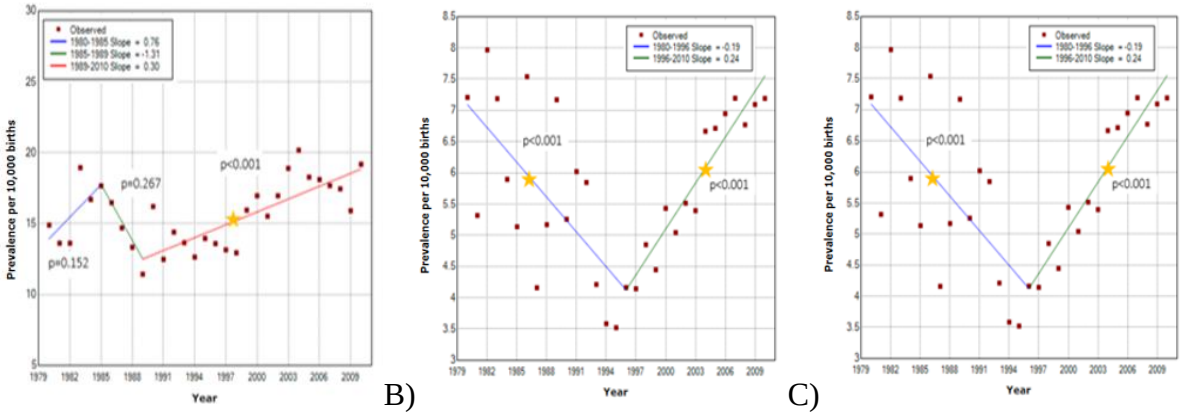
[b] Programs for which the degree of severity was unspecified in ≥80% of cases were excluded

Supplemental Figure 1. Trends in the international total prevalence of hypospadias for 27 ICBDSR programs using joinpoint regression, 1980-2010.[a]




[a] Stars indicate joinpoints with statistically significant ($p<0.05$) trends.

Supplemental Figure 2. Trends in the international total prevalence of hypospadias by clinical degree of severity among 7 ICBDSR programs with select characteristics,[a] 1980-2010.[b]

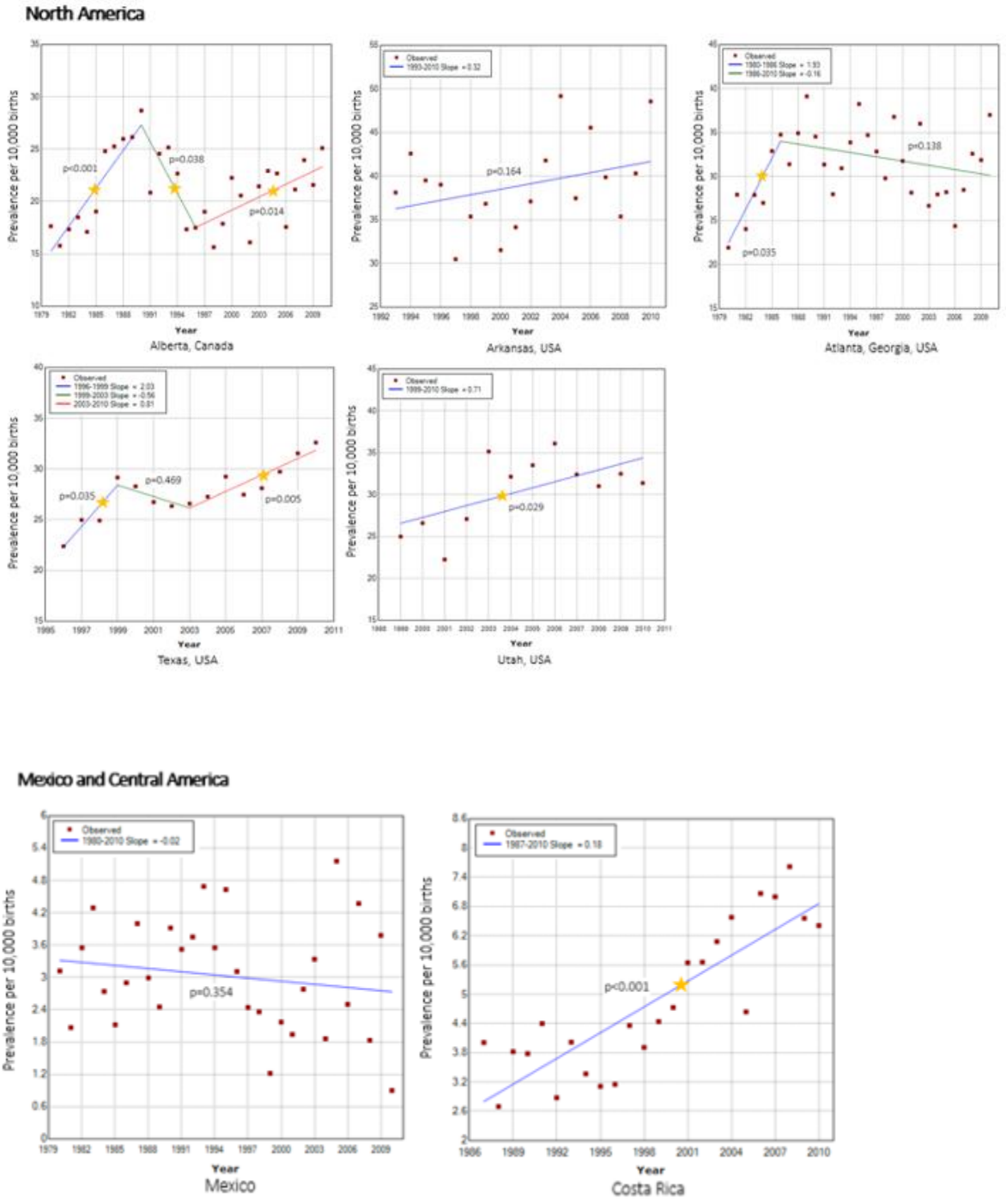



A) First-degree hypospadias, B) second-degree hypospadias, and C) third-degree hypospadias

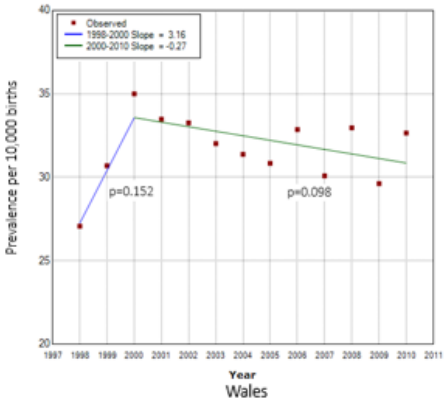
[a] Programs with 1) the clinical degree of severity specified in ≥80% of cases, 2) population-based ascertainment, 3) age of ascertainment ≥1 year, and 4) ascertainment from multiple sources.

[b] Stars indicate joinpoints with statistically significant ($p<0.05$) trends.

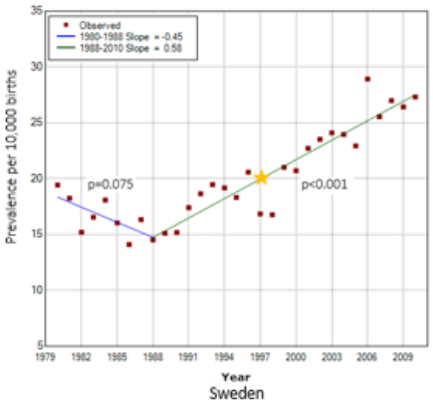
Supplemental Figure 3. Trends in the total prevalence of hypospadias by ICBDSR program, 1980-2010.[a, b]



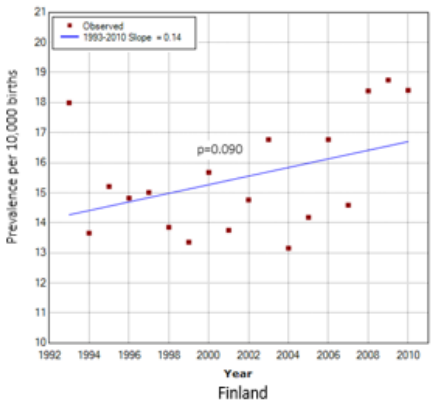
**Northern Europe**



Wales

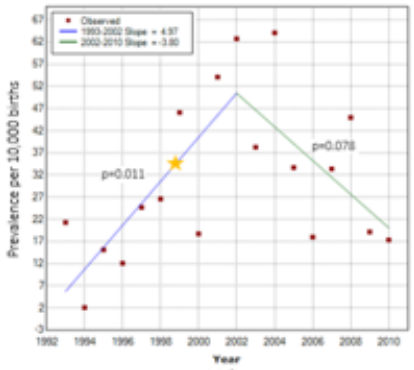


Sweden

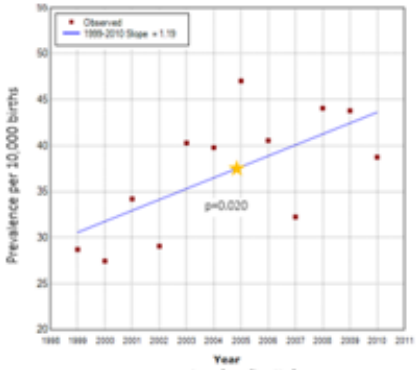


Finland

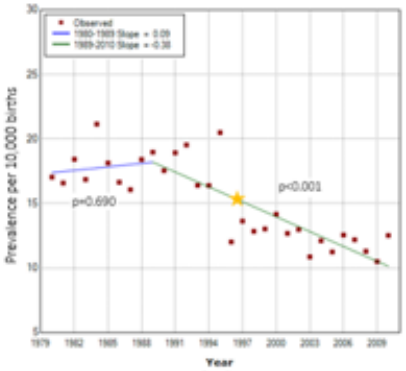
**Southern Europe**



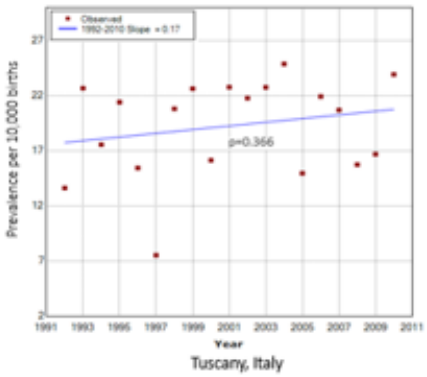
Malta



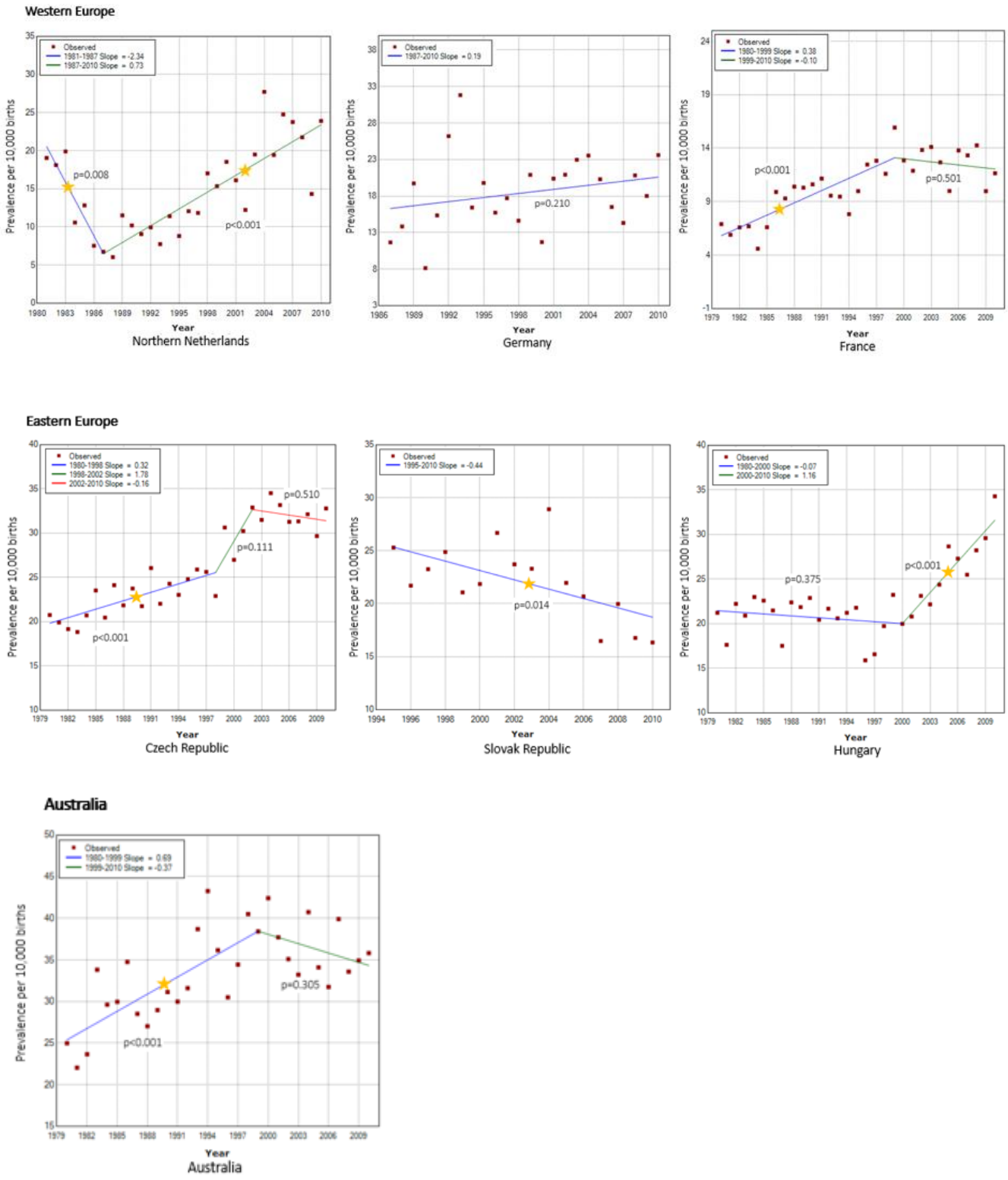
Lombardia, Italy



Spain



Tuscany, Italy




[a] Stars indicate joinpoints with statistically significant ($p<0.05$) trends.

[b] Joinpoint regression was not performed for programs with <11 years of data (Argentina, Colombia, Chile, Canada [National], Iran) or any years of missing data during the period analyzed (New Zealand).

**Appendix A. Details of case surveillance and selection methods**

The International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) was created for the purpose of collecting and sharing data across individual birth defects surveillance programs worldwide. When new research projects are initiated by the ICBDSR or proposed by its members, a specific study protocol is approved and each program is invited to participate by providing existing data for that specific analysis, if not available from regular monitoring of birth defects. We obtained aggregate-level data on hypospadias from 27 birth defect surveillance programs in the ICBDSR. Since each program had data for a potentially different study period, we chose the study period to be births from 1980 to 2010, years for which the majority of programs had more complete data. Surveillance methods and case definitions also vary between programs (18, 28). For example, for some programs, case identification is based on review of records by program staff for all births and terminations of pregnancy at all hospitals and delivery centers in the program's region, whereas surveillance for other programs relies on clinician reporting of cases to the program.

Programs identified cases based on infants with a recorded hypospadias diagnosis using the WHO International Classification of Diseases, ICD-9 (752.6) or ICD-10 (Q54) codes, in addition to reviewing the original birth defect descriptions. A British Pediatric Association (BPA) code extension for the ICD-9 code was used to differentiate hypospadias (752.60) from epispadias (752.61) and congenital chordee alone (752.62). The Royal College of Paediatrics and Child Health adaptation was used to identify the respective subtypes for ICD-10 codes. Thus, all systems could distinguish between hypospadias and epispadias or congenital chordee alone, which were not included in the study.

Cases among live births and stillbirths were included by all programs. Elective terminations of pregnancy for fetal anomaly (ETOPFA) were included by programs where terminations were permitted, except the hospital-based Spanish program. (This should not have strongly impacted the results since the prenatal diagnosis of hypospadias is very rare, and ~90% of the cases are isolated.) For each program, data were available for the total number of cases with hypospadias (live births, stillbirths, and ETOPFA) during each year of surveillance and the total number of births (live births and still births) in the same surveillance region during each respective year.

When available, we also received data on the number of cases with hypospadias by the degree of severity (first-degree, second-degree, third-degree, or degree unspecified) during each respective year. To increase consistency, programs were asked to classify glandular or coronal forms of hypospadias as first-degree hypospadias; subcoronal, distal penile, midshaft or proximal penile forms as second-degree hypospadias; and meatus openings on the scrotum or below (including penoscrotal or perineal hypospadias) as third-degree hypospadias. In addition, we reviewed information with each program's leadership about their surveillance program, including the percentage of cases without available data on the degree of severity, the length of the ascertainment period after birth (e.g., inclusion of only diagnoses made before 1 year of age), whether the program used population-based (e.g., as opposed to hospital-based) case identification, and whether case diagnoses involved confirmation across multiple sources (e.g., diagnosis on more than one medical record).

To better interpret the observed results, we also queried the director of each program for insights into the prevalence and trend results for their program. We specifically asked: (1) How do you interpret your total prevalence of hypospadias being in the 1st / 2nd / 3rd/ 4th quartile?

(2) How do you interpret the increase / decrease observed in the joinpoint regression analysis of your program? These responses were used to interpret the results and organize the discussion of this paper.